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(54) Quarternary Derivatives of Noroxymorphone Which Relieve Nausea and Emesis

(72) Goldberg, Leon I. , U.S.A.

(73) University of Chicago , U.S.A.

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# QUATERNARY DERIVATIVES OF NOROXYMORPHONE WHICH RELIEVE NAUSEA AND EMESIS

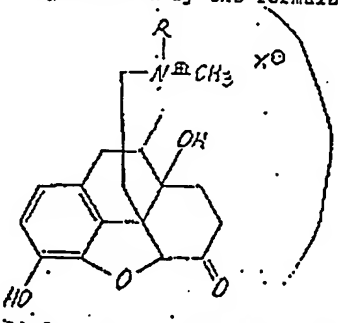
The administration of therapeutic doses of morphine and other clinically useful narcotic analgesics is often accompanied by unpleasant side effects on the gastro-intestinal system. For instance, morphine and related opiates such as meperidine and methadone may retard intestinal mobility by causing contractions of the small bowel circular smooth muscle.

Morphine and related narcotics may also induce nausea and increased mobility of the gastro-intestinal tract resulting in emesis or vomiting. These side effects are caused by direct stimulation of the chemoreceptor trigger zone for emesis in the area postrema of the medulla. (Goodman and Gilman, The Pharmacological Basis of Therapeutics, p. 502 (6th ed. 1980)). Studies have shown that morphine and other narcotics cause emesis in dogs. For example, Wang and Glaviano, JPET 111:329-334 (9143), reported that administration of 0.5 mg/kg of morphine intravenously to 12 dogs resulted in emesis in 9 dogs within an average of 2.4 minutes. (Mg/kg refers to milligrams of morphine per kilograms of body weight.) When 1.0 mg/kg of

morphine was administered intramuscularly to 13 dogs, 12 of them vomited within an average time of 3.5 minutes.

U. S. Patent No. 4,176,186 to myself and others disclosed treatment of intestinal immobility associated with the use of narcotic analgesics through the administration of quaternary derivatives of noroxymorphone. It has now been discovered that the same compounds are also useful for the treatment, both prophylactic and therapeutic, of the nausea and vomiting associated with the administration of these drugs.

According to the invention, therefore, nausea and vomiting by warm-blooded animals receiving morphine and related opiates, meperidine, methadone or the like, may be prevented or relieved by the administration of methylnaltrexone or other quaternary derivatives of noroxymorphone represented by the formula:




wherein

R is allyl or a related radical such as chloroallyl, cyclopropyl-methyl or propargyl, and

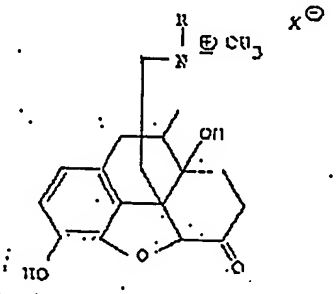
X is the anion of an acid, especially a chloride, bromide, iodide or methylsulfate anion.

These compounds are administered to the animal either prior to or simultaneously with the administration of the narcotic analgesic. They may be

administered either enterally or parenterally. There has not been observed any interference with the analgesic activity of the opiates.

As used herein, unless the sense of the usage indicates otherwise, the term "morphine" refers to any narcotic analgesic.

This invention relates to the use of quaternary derivatives of noroxymorphone to prevent or relieve nausea and vomiting associated with the administration of morphine to warm-blooded animals. The useful compounds are represented by the formula:



wherein

R is allyl or a related radical such as chloroallyl, cyclopropyl-methyl or propargyl, and

X is the anion of an acid, especially a chloride, bromide, iodide or methylsulfate anion.

The compounds are synthesized as described in United States Patent No. 4,176,186. A particularly preferred noroxymorphone derivative is methylnaltrexone, but other compounds represented by the above formula are also suitable.

Methylnaltrexone or other noroxymorphone derivatives may be administered to the patient either

enterally or parenterally. However, a preferred method of administration is by injection. Nausea and emesis may follow after even a single dose of morphine, unlike intestinal immobility which is usually the effect of chronic repeated usage of the drug. Consequently, it is contemplated that the patient will be given an injection of methylnaltrexone prior to surgery or other occasion when morphine is used to treat acute pain.

As illustrated by the following Controls and Examples, our studies show that methylnaltrexone inhibits emesis when administered either together with the morphine or before the morphine is administered. It is thought that methylnaltrexone or other quaternary noroxymorphone derivatives may be administered up to two hours before the administration of morphine, but that period may be variable. In our studies, methylnaltrexone was administered intramuscularly by means of a syringe. Methylnaltrexone may also be administered enterally or parenterally by other means. It has been found to be effective in dosages in the range of about 0.05 mg/kg to about 1.0 mg/kg for each 1 mg/kg of administered morphine. It was found effective when administered in the same syringe as morphine and also when administered up to about one hour before the administration of morphine.

The effect of methylnaltrexone in reversing the emetic effects of morphine is illustrated herein. The unit of mg/kg refers to milligrams of substance administered per kilograms of body weight.

CONTROL 1 AND EXAMPLE 1

One mg/kg of morphine was administered intramuscularly to five dogs. Four dogs vomited. In each instance, vomiting occurred within four minutes. On a different day the same dose of morphine was

administered intramuscularly to the same five dogs in the same syringe with 1 mg/kg of methylnaltrexone. None of the dogs vomited.

CONTROL 2 AND EXAMPLE 2

Six dogs were given intramuscular doses of 1 mg/kg of morphine. All six dogs vomited. On an additional day the same dose of morphine was combined with 0.5 mg/kg of methylnaltrexone and administered in the same syringe to the same dogs. None of the dogs vomited.

CONTROL 3 AND EXAMPLE 3

One mg/kg of morphine was administered intramuscularly to three dogs. All three dogs vomited. On an additional day the morphine was combined with 0.25 mg/kg of methylnaltrexone and administered in the same syringe. None of the dogs vomited.

CONTROL 4 AND EXAMPLE 4

Methylnaltrexone was administered to two dogs prior to the administration of 1 mg/kg morphine. In one dog, 0.5 mg/kg of methylnaltrexone was administered intramuscularly 15 minutes before the morphine. No vomiting occurred. In the second dog, the same dose of methylnaltrexone was administered 30 minutes before the administration of morphine. No vomiting occurred.

CONTROL 5 AND EXAMPLE 5

0.05 mg/kg methylnaltrexone was administered intravenously to four dogs one minute prior to the administration of 1.0 mg/kg morphine. No vomiting occurred in any of the dogs. On a different day, the same animals were given 1.0 mg/kg morphine without the administration of methylnaltrexone. All four dogs vomited.

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The administration of methylnaltrexone alone was found to produce no noticeable effects in the animals. Previous studies with larger doses of methylnaltrexone have demonstrated that unlike the non-quaternary naltrexone, methylnaltrexone does not precipitate withdrawal systems in morphine-tolerant dogs. Russell et al., Eur. J. Pharmacol. 78:255-261 (1982). Methylnaltrexone has not been found to interfere with the analgesic activity of morphine or naroxtion.

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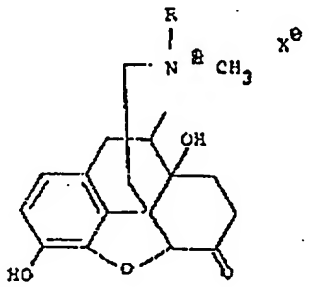
THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. Use of a compound of the formula:



wherein

R is allyl or a related radical; and

X is the anion of an acid;

prior to or simultaneously with administration of a narcotic analgesic to prevent or relieve nausea and emesis associated with the use of the narcotic analgesics in warm-blooded animals.

2. Use as claimed in claim 1 in which R is chloroallyl, cyclopropyl-methyl or propargyl.

3. Use as claimed in claim 1 in which X is a choride, bromide, iodide or methylsulfate anion.

4. Use as claimed in claim 1, where the compound is is in an amount between 0.05 mg/kg and about 1.0mg/kg of animal body weight.

5. Use as claimed in claim 1, as an enterally administered compound.

6. Use as claimed in claim 1, as parenterally administered compound.

7. Use as claimed in claim 6, as an injectably administered compound.

8. Use as claimed in claim 1, prior to the administration of the narcotic analgesic.

9. Use as claimed in claim 1, up to about two hours prior to the administration of the narcotic analgesic.

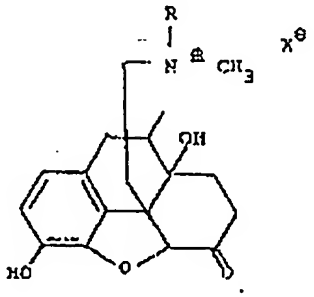
10. Use as claimed in claim 1, concurrently with the administration of the narcotic analgesic.

11. Use of methylnaltroxone to prevent or relieve nausea and emesis associated with the use of a narcotic analgesic in war-blooded animals.

12. Use as claimed in claim 11 in an amount of between 0.05 mg/kg of animal body weight and about 1.0 mg/kg of animal body weight simultaneously with or up to about two hours prior to the time of administration of the narcotic analgesic.

13. Use as claimed in claim 12, as a parenterally administered compound.

14. A pharmaceutical composition for preventing or relieving nausea and emesis comprising a narcotic analgesic in combination with at least one quaternary derivative of noroxymorphone:



wherein

R is allyl or a related radical; and

X is the anion of an acid;

and wherein the quaternary derivative of noroxymorphone is present in an amount effective to prevent or relieve nausea induced by the narcotic analgesic.

15. A pharmaceutical composition as claimed in claim 12 in which R is chloroallyl, cyclopropyl-methyl or propargyl.

16. A composition as claimed in claim 12 in which X is a chloride, bromide, iodide or methylsulfate anion.

17. A composition according to claim 14, wherein the quaternary derivative of noroxymorphone is present in a unit dose of between about 0.05 mg and about 1.0 mg for each 1 mg of morphine.

18. A composition as claimed in claim 14, wherein the narcotic analgesic is morphine.

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19. A composition as claimed in claim 14, wherein the quaternary derivative of noroxymorphone is methylnaltrexone.

# QUATERNARY DERIVATIVES OF NOROXYMORPHONE WHICH RELIEVE NAUSEA AND EMESIS

## ABSTRACT OF THE DISCLOSURE

Quaternary derivatives of noroxymorphone are used to prevent or relieve nausea and emesis associated with the use of narcotic analgesics without interfering with the analgesic activity of the drugs. A particularly preferred compound is methylnaltrexone. The compound is administered in a concentration between 0.05 mg/kg and 1.0 mg/kg prior to or concurrently with the administration of the narcotic analgesic.

SUBSTITUTE

*REMPLACEMENT*

SECTION is not Present

*Cette Section est Absente*